JACC: CARDIOVASCULAR INTERVENTIONS VOL. 4, NO. 8, 2011

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

DOI: 10.1016/j.jcin.2011.03.017

2-Year Clinical Follow-Up From the Randomized Comparison of Biolimus-Eluting Stents With Biodegradable Polymer and Sirolimus-Eluting Stents With Durable Polymer in Routine Clinical Practice

Volker Klauss, MD,* Patrick W. Serruys, MD,§ Thomas Pilgrim, MD,¶ Pawel Buszman, MD,§§ Axel Linke, MD,‡ Thomas Ischinger, MD,† Franz Eberli, MD,†† Roberto Corti, MD,‡‡ William Wijns, MD,‖‖ Marie-Claude Morice, MD,¶¶ Carlo di Mario, MD,## Robert Jan van Geuns, MD,§ Gerrit-Anne van Es, PhD,‖ Bindu Kalesan, PhD,¶# Peter Wenaweser, MD,¶ Peter Jüni, MD,#** Stephan Windecker, MD¶**

Munich and Leipzig, Germany; Rotterdam, the Netherlands; Bern and Zurich, Switzerland; Katowice, Poland; Aalst, Belgium; Paris, France; and London, United Kingdom

Objectives This study sought to investigate safety and efficacy of biolimus-eluting stents (BES) with biodegradable polymer as compared with sirolimus-eluting stents (SES) with durable polymer through 2 years of follow-up.

Background BES with a biodegradable polymer provide similar efficacy and safety as SES with a durable polymer at 9 months. Clinical outcomes beyond the period of biodegradation of the polymer used for drug release and after discontinuation of dual antiplatelet therapy are of particular interest.

Methods A total of 1,707 patients were randomized to unrestricted use of BES (n = 857) or SES (n = 850) in an all-comers patient population.

Results At 2 years, BES remained noninferior compared with SES for the primary endpoint, which was a composite of cardiac death, myocardial infarction, or clinically indicated target vessel revascularization (BES 12.8% vs. SES 15.2%, hazard ratio [HR]: 0.84, 95% confidence interval [CI]: 0.65 to 1.08, $p_{noninferiority} < 0.0001$, $p_{superiority} = 0.18$). Rates of cardiac death (3.2% vs. 3.9%, HR: 0.81, 95% CI: 0.49 to 1.35, p = 0.42), myocardial infarction (6.3% vs. 5.6%, HR: 1.12, 95% CI: 0.76 to 1.65, p = 0.56), and clinically indicated target vessel revascularization (7.5% vs. 8.6%, HR: 0.86, 95% CI: 0.62 to 1.20, p = 0.38) were similar for BES and SES. The rate of definite stent thrombosis through 2 years was 2.2% for BES and 2.5% for SES (p = 0.73). For the period between 1 and 2 years, event rates for definite stent thrombosis were 0.2% for BES and 0.5% for SES (p = 0.42). After discontinuation of dual antiplatelet therapy, no very late definite stent thrombosis occurred in the BES group.

Conclusions At 2 years of follow-up, the unrestricted use of BES with a biodegradable polymer maintained a similar safety and efficacy profile as SES with a durable polymer. (Limus Eluted From a Durable Versus Erodable Stent Coating [LEADERS]; NCT00389220) (J Am Coll Cardiol Intv 2011;4: 887–95) © 2011 by the American College of Cardiology Foundation

From the *Department of Cardiology, University Hospital Munich (Innenstadt), Munich, Germany; †Department of Cardiology, Hospital Bogenhausen, Munich, Germany; ‡Herzzentrum Leipzig, Leipzig, Germany; §Thoraxcenter, Erasmus University, Rotterdam, the Netherlands; ‖Cardialysis, Rotterdam, the Netherlands; ¶Department of Cardiology, Bern University Hospital, Bern, Switzerland; #Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; **Clinical Trials Unit Bern, Bern University Hospital, Bern, Switzerland; ††Department of Cardiology, Triemli Spital, Zurich, Switzerland; ‡‡Department

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 8, 2011
AUGUST 2011:887–95

Early generation drug-eluting stents (DES) releasing either sirolimus or paclitaxel from durable polymer surface coatings have been shown to reduce angiographic and clinical restenosis compared with bare-metal stents (1–3). However, concerns arose that early generation DES are associated with an increased risk of very late (>1 year) stent thrombosis (4,5). Delayed healing and re-endothelialization as well as chronic inflammation and hypersensitivity reactions have been identified as pathophysiological mechanisms leading to very late stent thrombosis and may be related at least in part to the permanent polymer coating (6,7). With the aim to further improve the safety and efficacy of DES, a biolimus-eluting stent (BES) has been designed with a biodegradable polymer applied to the stent's abluminal surface, which is metabolized to water and carbon dioxide within 6 to 9 months. Biolimus is a highly lipophilic sirolimus analog, which inhibits the mammalian target of rapamycin, and inhibits smooth muscle cell proliferation by causing the arrest of the cell cycle at G_0 with similar potency to sirolimus (8).

BES with biodegradable polymer coating have previously been shown to be noninferior to a SES with durable polymer in terms of major adverse cardiovascular events at 9-month follow-up in the randomized LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial (9). Longer-term follow-up beyond the period of biodegradation of the polymer used for drug release and after discontinuation of dual antiplatelet therapy is of particular interest to determine the late safety profile of this platform. We therefore investigated the clinical outcomes of patients included into this study through 2 years with particular attention to the time period after discontinuation of mandatory dual antiplatelet therapy.

Abbreviations and Acronyms

BES = biolimus-eluting stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)

Methods

Study population. The methods of the LEADERS trial have been published previously (9). In brief, the study applied an all-comers approach recruiting 1,707 patients with chronic stable coronary artery disease or acute coronary syndromes including ST-segment elevation myocardial infarction, who were eligible for enrollment if they had ≥1 lesion with diameter stenosis ≥50% and a reference vessel diameter 2.25 to 3.5 mm. Selection criteria were broad, reflecting routine clinical practice. We set no limit for the number of treated lesions, vessels, or lesion length, and excluded no patients on the basis of comorbidity apart from the following pre-specified criteria: known allergy to acetylsalicylic acid, clopidogrel, heparin, stainless steel, sirolimus, biolimus, or contrast material; planned surgery within 6 months of percutaneous coronary intervention (PCI) unless the dual antiplatelet therapy could be maintained throughout the perisurgical period; pregnancy; participation in another trial before reaching the primary endpoint; and inability to provide informed consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

Randomization and procedures. Patients were randomly allocated on a 1:1 basis to treatment with a stent eluting biolimus-A9 with a biodegradable polymer, polylactic acid (BioMatrix Flex, Biosensors Inc., Newport Beach, California) or a sirolimus-eluting stent (SES) with a durable polymer (Cypher Select, Cordis, Miami Lakes, Florida) and to active angiographic follow-up at 9 months or clinical follow-up only on a 1:3 basis using a factorial design. BES were available in diameters of 2.25 to 3.5 mm and in lengths of 8 to 28 mm, whereas SES were available in diameters of 2.25 to 3.5 mm and in lengths of 8 to 33 mm. Balloon angioplasty and stent implantation were performed according to standard technique, and direct stenting was allowed. Procedural anticoagulation was achieved with unfractionated heparin 5,000 IU or 70 to 100 IU/kg, whereas the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. All patients enrolled into the study received ≥75 mg of acetylsalicylic acid and at least 300 mg of clopidogrel before the procedure. All patients were discharged on ≥75 mg of acetylsalicylic acid indefinitely and clopidogrel 75 mg for a minimum of 12 months following the index procedure. In the case of intercurrent revascularization procedures needing stent implantation, cardiologists were encouraged to use study stents.

Follow-up. Adverse events were assessed in the hospital, and clinical follow-up was performed at 1, 6, 9, 12, and

of Cardiology, University Hospital, Zurich, Switzerland; §§Department of Cardiology, Medical University of Silesia, Katowice, Poland; ‖‖Department of Cardiology, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; ¶¶Department of Cardiology, Institut Cardiovasculaire Paris-Sud, Paris, France; and the ##Department of Cardiology, Royal Brompton Hospital, London, United Kingdom. Dr. Linke has received consulting fees from Medtronic. Dr. Eberli has received honoraria from Cordis and Biosensors and research grants from Abbott, Biosensors, Boston Scientific, and Terumo. Dr. Morice has been a board member or served on the Speakers' Bureau for Boston Scientific, Cordis, Medtronic, and Biosensors. Dr. di Mario has received a research grant from Biosensors. Dr. Wenaweser has received lecture fees from Cordis. Dr. Jüni has been an unpaid member of steering groups and/or planning committees of cardiovascular trials funded by Abbott Vascular, Biosensors, Cordis, Medtronic, and St. Jude Medical. Dr. Windecker has received research grants from Abbott, Boston Scientific, Biosensors, Cordis, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. John Hirshfeld, Jr., MD, served as Guest Editor for this paper.

Manuscript received November 22, 2010; revised manuscript received February 14, 2011, accepted March 18, 2011.

24 months. Additional clinical follow-up is planned at yearly intervals to 5 years. One in 4 patients was asked to return for angiographic follow-up at 9 months.

Study endpoints. The primary clinical endpoint of this study was the composite of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization. The detailed definitions of these endpoints have been reported previously (9). Secondary endpoints included any target lesion revascularization (clinically indicated or nonclinically indicated); cardiac death; death from any cause; myocardial infarction; stent thrombosis according to definitions of the Academic Research Consortium (10). A blinded independent clinical events committee adjudicated all endpoints, and independent study monitors verified all case reports from data on site. The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type. Angiography films were centrally assessed at 1 angiographic core laboratory (Cardialysis, Rotterdam, the Netherlands) with assessors unaware of the allocated stent.

Statistics. This was a noninferiority trial, which was powered for noninferiority on the primary clinical endpoint at 9 months. Based on event rates reported for the BASKET (Basel Stent Cost-Effectiveness Trial) (11) and SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) (12) trials in patients comparable to those to be included in this trial, we expected rates of the primary endpoint at 9 months to be 8% in both treatment groups. Noninferiority would be declared if the upper limit of the 1-sided 95% confidence interval (CI) of the absolute risk difference did not exceed 4%. Using a simulation-based approach with 10,000 simulations, with a continuity-corrected modification of the Wilson score method to estimate confidence intervals for binary data (13), we estimated that 850 patients per group yielded >90% power to detect noninferiority at a 1-sided type I error of 0.05. After establishing noninferiority, we calculated regular 2-sided 95% CI and 2-sided p values to allow conventional interpretation of results as if using a superiority design.

In the present analysis, the 2-year results are reported. Continuous variables are expressed as mean ± SD; and categorical data are presented as frequency (percentages). We used Mantel-Cox method to calculate rate ratios and 95% CI for comparisons of clinical outcomes between groups, and the log-rank test to calculate corresponding p values. Survival curves were constructed for time-to-event

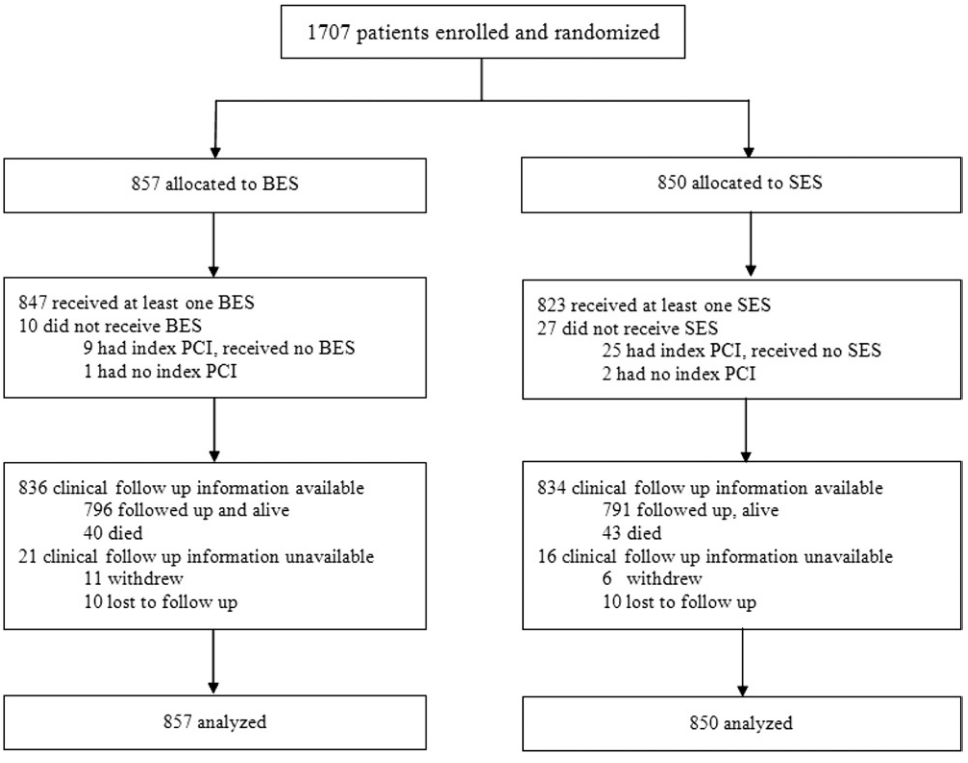

Figure 1. Flow Chart of Clinical Follow-Up of Patient Population

Patient flow of the patients through the trial up to 2 years. BES = biolimus-eluting stent(s); PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 8, 2011
AUGUST 2011:887–95

Table 1. Baseline Clinical and Angiographic Characteristics

	BES (n = 857)	SES (n = 850)
Age, yrs	64.6 ± 10.8	64.5 ± 10.7
Male	643 (75.0%)	634 (74.6%)
Body mass index, kg/m^2, mean	27.6	27.5
Diabetes mellitus	223 (26.0%)	191 (22.5%)
Hypertension	630 (73.5%)	618 (72.7%)
Hypercholesterolemia	560 (65.3%)	580 (68.2%)
Current smoker	206 (24.0%)	214 (25.2%)
Family history of CAD	339 (39.6%)	374 (44.0%)
Previous MI	276 (32.2%)	277 (32.6%)
Previous PCI	312 (36.4%)	312 (36.7%)
Previous CABG	90 (10.5%)	107 (12.6%)
Previous stroke	40 (4.7%)	28 (3.3%)
Peripheral vascular disease	70 (8.2%)	63 (7.4%)
Multivessel disease	209 (24.4%)	176 (20.7%)
Left ventricular ejection fraction, %*	55.9 ± 11.3	55.4 ± 12.4
SYNTAX score†	13.2	13.3
Acute coronary syndrome	470 (54.8%)	473 (55.7%)
ST-segment elevation MI	135 (15.8%)	140 (16.5%)
Non–ST-segment elevation MI	145 (16.9%)	153 (18.0%)
Unstable angina	190 (22.2%)	180 (21.2%)
Stable angina	387 (45.2%)	377 (44.4%)
Silent ischemia	89 (10.4%)	85 (10.0%)
De-novo lesions	1,181/1,256 (94.0%)	1,126/1,213 (92.9%)
Off-label use	696 (81.2%)	665 (78.2%)
Small-vessel disease, RVD <2.75 mm	585 (68.3%)	568 (66.8%)
Lesions >20 mm	262 (30.6%)	225 (26.5%)
RVD, mm‡	2.60 ± 0.61	2.60 ± 0.57
Minimum lumen diameter, mm§	0.91 ± 0.50	0.95 ± 0.52
Diameter stenosis, %§	64.6 ± 17.9	63.3 ± 18.2

Values are mean ± SD or n (%). *Left ventricular ejection fraction is available for 601 BES and 607 SES patients. †SYNTAX score is for 678 patients in the BES group and 673 in the SES group. ‡RVD was assessed for 1,246 patients in the BES group and 1,199 in the SES group. §Minimum lumen diameter was assessed for 1,209 patients in the BES group and 1,186 in the SES group.

BES = biolimus-eluting stent(s); CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; SES = sirolimus-eluting stent(s); SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery trial.

variables using Kaplan-Meier estimates. Stratified analyses according to the presence or absence of diabetes, acute coronary syndrome, acute ST-segment elevation myocardial infarction, left anterior descending artery, multivessel disease, off-label use, de-novo lesions, small-vessel disease, and long-lesions were carried out. To identify possible interaction between treatment effect and these characteristics, the chi-square test was used to test for effect modification. A dedicated statistician performed all analyses using SAS (version 8.02, SAS Institute Inc., Cary, North Carolina). All p values and CI were 2-sided except for noninferiority of BES compared with SES for the primary endpoint.

Results

Figure 1 shows the flow of patients from enrollment to 2 years on an intention-to-treat basis. Overall, clinical follow-up was available in 1,670 patients (97.5%): 836 of 857 BES patients (97.1%), and 834 of 850 SES patients (98.1%). The baseline clinical and angiographic characteristics were similar in both groups (Table 1). There was no significant difference in procedural characteristics between both groups.

Clinical outcomes at 2 years. Table 2 shows clinical outcomes at 2 years. The primary endpoint occurred in 110 (12.8%) BES patients and 129 (15.2%) SES patients (Fig. 2). Noninferiority of BES compared with SES was maintained at 2 years with an absolute risk difference of −2.4%, the boundary of the 1-sided 95% CI at 0.5%, and the corresponding 1-sided p value for noninferiority at <0.0001. Superiority testing of the primary endpoint yielded nonsignificant differences between BES and SES (p = 0.18) (Table 2). The use of BES compared with SES was associated with similar rates of cardiac death (3.2% vs. 3.9%; hazard ratio [HR]: 0.81; 95% CI: 0.49 to 1.35; p = 0.42) and myocardial infarction (6.3% vs. 5.6%; HR: 1.12; 95%

Table 2. Clinical Outcomes at 2 Years

Event	BES (n = 857)	SES (n = 850)	HR (95% CI)	p Value
Death	40 (4.7)	43 (5.1)	0.92 (0.60–1.42)	0.71
Cardiac death	27 (3.2)	33 (3.9)	0.81 (0.49–1.35)	0.42
Myocardial infarction	54 (6.3)	48 (5.6)	1.12 (0.76–1.65)	0.56
Q-wave	4 (0.5)	8 (0.9)	0.49 (0.15–1.64)	0.25
Non–Q-wave	50 (5.8)	41 (4.8)	1.22 (0.81–1.84)	0.35
Clinically indicated TLR	55 (6.4)	60 (7.1)	0.90 (0.63–1.30)	0.59
Percutaneous	50 (5.8)	55 (6.5)	0.90 (0.61–1.32)	0.58
Surgical	8 (0.9)	9 (1.1)	0.88 (0.34–2.28)	0.79
Any TLR	68 (7.9)	74 (8.7)	0.91 (0.65–1.26)	0.55
Percutaneous	61 (7.1)	67 (7.9)	0.90 (0.64–1.27)	0.55
Surgical	11 (1.3)	13 (1.5)	0.84 (0.38–1.87)	0.67
Clinically indicated TVR	64 (7.5)	73 (8.6)	0.86 (0.62–1.20)	0.38
Percutaneous	58 (6.8)	66 (7.8)	0.86 (0.61–1.23)	0.42
Surgical	10 (1.2)	12 (1.4)	0.83 (0.36–1.91)	0.65
Any TVR	83 (9.7)	96 (11.3)	0.85 (0.63–1.13)	0.26
Percutaneous	73 (8.5)	83 (9.8)	0.86 (0.63–1.18)	0.36
Surgical	15 (1.8)	19 (2.2)	0.78 (0.40–1.53)	0.47
Any repeat revascularization	83 (9.7)	99 (11.6)	0.82 (0.61–1.10)	0.18
Percutaneous	73 (8.5)	83 (9.8)	0.86 (0.63–1.18)	0.36
Surgical	15 (1.8)	22 (2.6)	0.67 (0.35–1.30)	0.24
Death or MI	82 (9.6)	85 (10.0)	0.96 (0.71–1.30)	0.79
Cardiac death or MI	70 (8.2)	76 (8.9)	0.92 (0.66–1.27)	0.60
Cardiac death, MI, or clinically indicated TLR	102 (11.9)	116 (13.6)	0.87 (0.67–1.13)	0.30
Cardiac death, MI, or clinically indicated TVR	110 (12.8)	129 (15.2)	0.84 (0.65–1.08)	0.18

Values are n (%).

CI = confidence interval; HR = hazard ratio; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

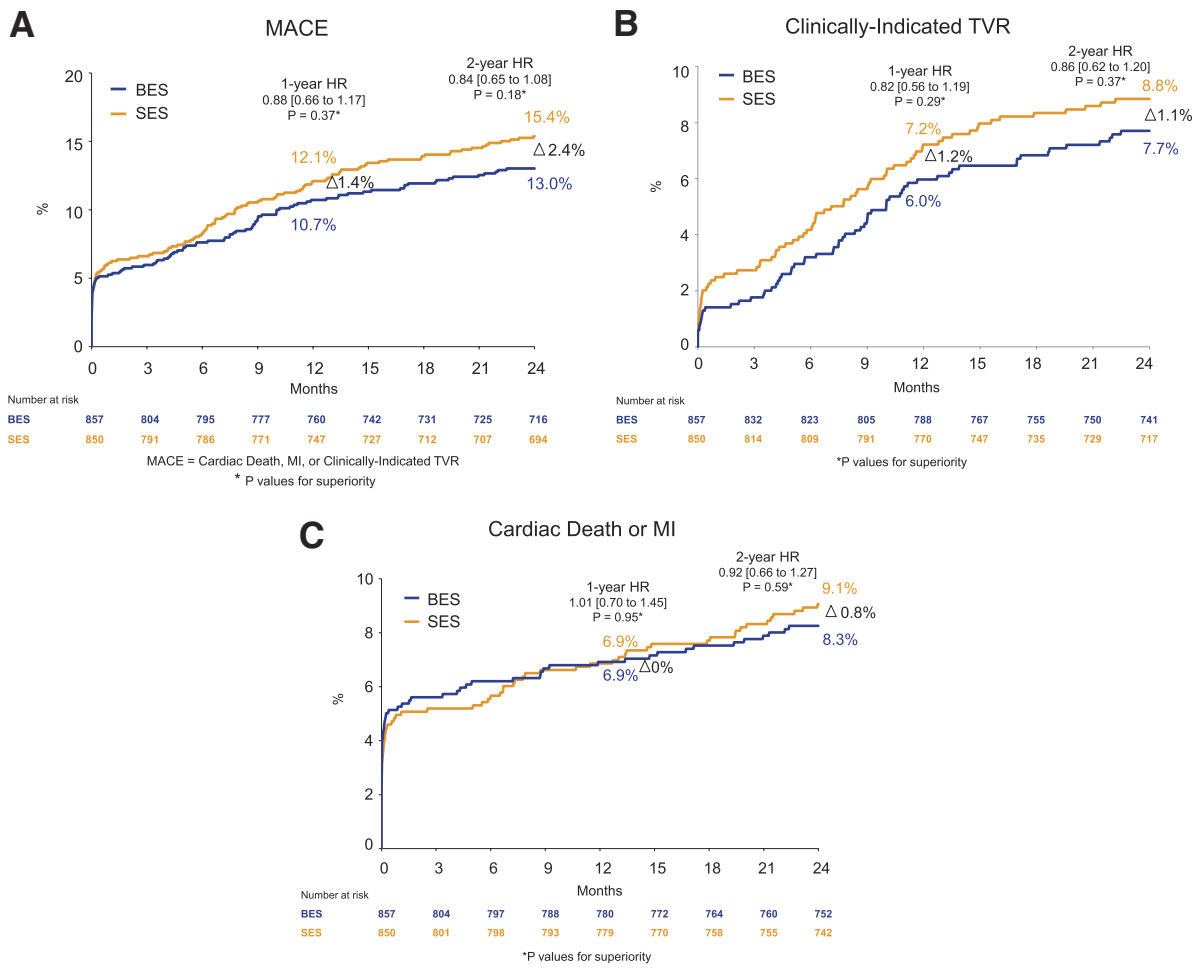

Figure 2. Clinical Outcome Up to 2 Years of Follow-Up

(A) Time-to-event curves are shown for the primary endpoint of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization up to 2 years of follow-up for the BES **(blue)** and the SES **(orange).** The p values are 2-sided from superiority testing using a log-rank test. **(B)** Time-to-event curves are shown for the endpoint of clinically indicated target vessel revascularization up to 2 years of follow-up for the BES **(blue)** and the SES **(orange).** The p values are 2-sided from superiority testing using a log-rank test. **(C)** Time-to-event curves are shown for the endpoint of cardiac death or myocardial infarction up to 2 years of follow-up for the BES **(blue)** and the SES **(orange).** The p values are 2-sided from superiority testing using a log-rank test. HR = hazard ratio; MACE = major adverse cardiac event(s); MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Figure 1.

CI: 0.76 to 1.65; p = 0.60). In addition, clinically indicated target vessel revascularization was comparable between BES and SES patients (7.5% vs. 8.6%; HR: 0.86; 95% CI: 0.62 to 1.20; p = 0.38) (Fig. 2).

The findings for the primary endpoint were consistent across the pre-specified stratified analyses for diabetes, acute coronary syndromes, and de novo lesions, as well as other subgroups including lesion in the left anterior descending artery, small-vessel disease, long lesions, and off-label use (Fig. 3). A significant interaction was observed between estimated HR and presence or absence of ST-segment elevation myocardial infarction at baseline (p for interaction = 0.02). A lower rate of major adverse cardiovascular events in BES compared with SES was apparent in patients with ST-segment elevation myocardial infarction (HR: 0.40, 95% CI: 0.20 to 0.80), but not in remaining patients (HR: 0.96, 95% CI: 0.73 to 1.27).

Stent thrombosis and antiplatelet therapy. The rates of stent thrombosis as per the Academic Research Consortium's definitions are listed in Table 3. There was no significant difference in definite, probable, or possible stent thrombosis during the early, late, or very late stent time period between both groups. There was 1 secondary definite late stent thrombosis in a SES patient at 60 days who experienced an early stent thrombosis at 3 days. Definite very late stent thrombosis occurred among 0.2%

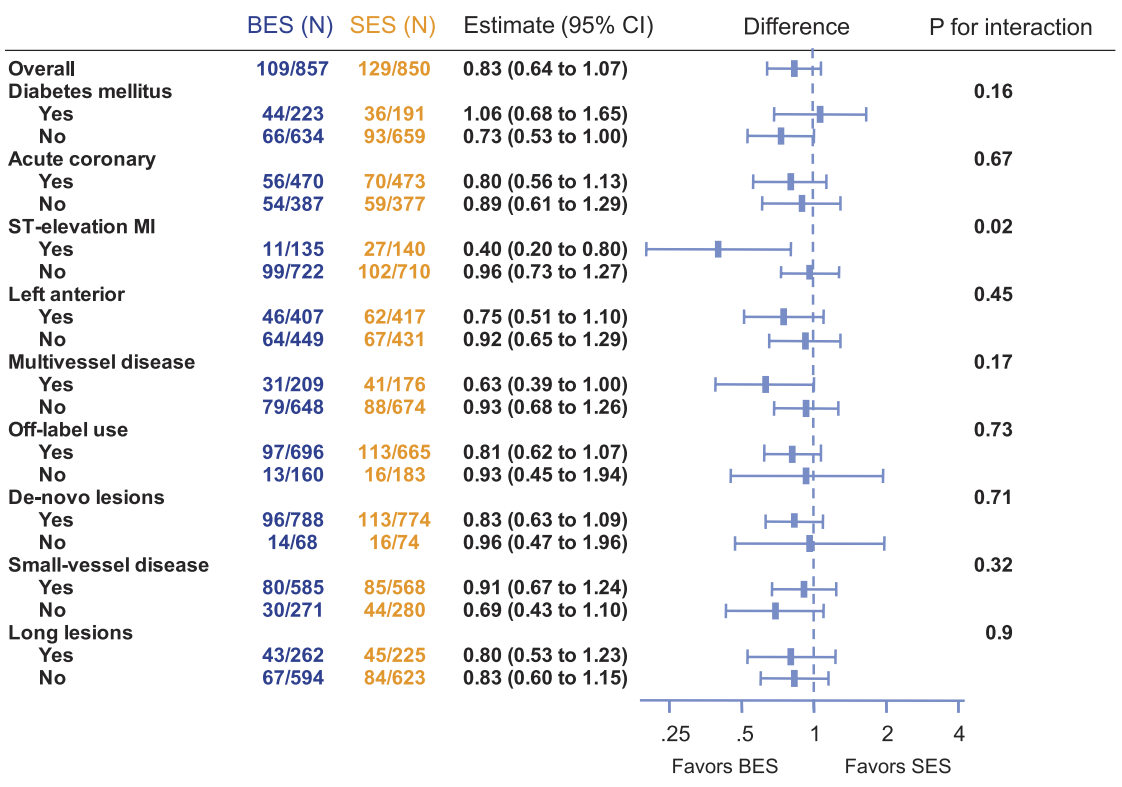

Figure 3. Stratified Analysis of the Primary Endpoint

Data are shown with relative risks and 95% confidence intervals (CI) for the primary endpoint at 2 years among subgroups of patients randomly assigned to BES or SES. The p value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. MI = myocardial infarction; other abbreviations as in Figure 1.

Table 3. Stent Thrombosis According to ARC Definitions

	BES (n = 857)	SES (n = 850)	p Value
Definite stent thrombosis			
Early	14 (1.6%)	14 (1.6%)	0.99
Late	3 (0.4%)	4 (0.5%)	0.70
Very late	2 (0.2%)	4 (0.5%)	0.42
Overall	19 (2.2%)	21 (2.5%)*	0.73
Probable stent thrombosis			
Early	5 (0.6%)	2 (0.2%)	0.28
Late	2 (0.2%)	0 (0.0%)	1.00
Very late	0 (0.0%)	0 (0.0%)	—
Overall	7 (0.8%)	2 (0.2%)	0.12
Possible stent thrombosis			
Early	0 (0.0%)	0 (0.0%)	—
Late	7 (0.8%)	9 (1.1%)	0.60
Very late	7 (0.8%)	8 (0.9%)	0.78
Overall	14 (1.6%)	17 (2.0%)	0.57
Definite or probable stent thrombosis			
Early	18 (2.1%)	16 (1.9%)	0.74
Late	5 (0.6%)	4 (0.5%)	0.75
Very late	2 (0.2%)	4 (0.5%)	0.42
Overall	25 (2.9%)	23 (2.7%)*	0.79

Values are n (%). The time periods are: early = 0–30 days; late = 31–360 days; very late = 361–720 days; overall = 0–720 days. *Excludes 1 definite secondary stent thrombosis, which occurred in a patient at 60 days, who had already experienced a stent thrombosis at 3 days.

ARC = Academic Research Consortium; other abbreviations as in Table 1.

of patients treated with BES and 0.5% of patients treated with SES (Fig. 4) between 1 and 2 years of follow-up. Table 4 summarizes the timing, lesion characteristics, clinical indication at baseline, clinical consequence, and relationship to dual antiplatelet therapy of very late definite stent thrombosis.

As shown in Table 5, aspirin use was high throughout the 2-year period. Per protocol, thienopyridine use was recommended for 12 months, but its use declined to 68.1% in the BES group and 66.5% in the SES group at 12 months and to 23.4% and 24.3% at 24 months, respectively. In 317 patients who discontinued dual antiplatelet therapy before 12 months, no definite stent thrombosis was observed in the BES group (0 of 154) compared with 1.2% in the SES group (2 of 163). Among the 963 patients who discontinued thienopyridine therapy after 12 months, very late stent thrombosis rate amounted to 0% in BES patients (0 of 484) and 0.6% in SES patients (3 of 479).

Discussion

This randomized study confirmed the efficacy and safety of BES with an abluminal biodegradable polymer compared

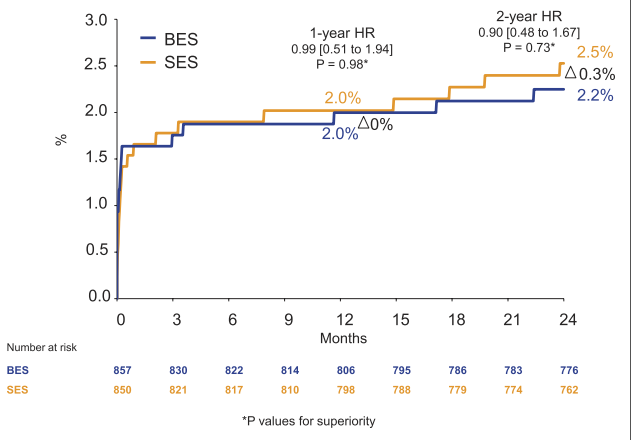

Figure 4. Definite Stent Thrombosis

Time-to-event curves for the endpoint of definite stent thrombosis up to 2 years of follow-up for the BES **(blue)** and the SES **(orange).** The p values are 2-sided from superiority testing using a log-rank test. HR = hazard ratio; other abbreviations as in Figure 1.

with SES with a durable polymer at 2 years of follow-up. The primary endpoint—a composite of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization—demonstrated noninferiority of BES to SES. Stent thrombosis continued to occur between 1 and 2 years in the BES group, but the overall incidence was low in this all-comer patient population, and there was no apparent relationship with the discontinuation of dual antiplatelet therapy.

Whereas most previous DES trials recruited patients with on-label characteristics, more than one-half of patients undergoing PCI with DES in routine clinical practice have at least 1 off-label characteristic (14). Of note, compared with standard use, early and late DES safety is inferior in patients with off-label characteristics, and the long-term effectiveness of DES is also inferior with both off-label and untested use (14,15). Consequently, the Circulatory System Devices Advisory Panel of the U.S. Food and Drug Administration underlined the need for conducting studies in off-label indications (16). The current study followed this recommendation and enrolled patients undergoing PCI with the unrestricted use of DES to reflect routine clinical practice. Most patients had an acute coronary syndrome and more than three-quarters of patients received 1 or more DES for an off-label indication. This may have contributed to the fact that the 2-year event rates reported in this study were somewhat higher than those observed in recent DES trials with lower risk profiles but comparable during the follow-up period (17,18). A recent study compared a second-generation everolimus-eluting stent with a first-generation paclitaxel-eluting stent in a similar patient population (COMPARE [Comparison of the Everolimus-Eluting Xience-V Stent With the Paclitaxel-Eluting Taxus Liberte Stent in All-Comers: A Randomized Open Label Trial]) (19). Overall, the everolimus-eluting stent was superior to the paclitaxel-eluting stent, and event rates at 1 year were lower for both stents than in the current trial. As COMPARE used a different comparator, it remains to be determined whether a comparison with sirolimus-eluting stents would have altered the results.

The use of early generation DES has been associated with increased rates of very late (beyond 1 year) stent thrombosis compared with bare-metal stents, a difference that emerged particularly in off-label indications (14,15,20,21). Although the occurrence of very late stent thrombosis remains largely unpredictable and no specific cause has been identified, the properties of the polymer used for controlled drug release may be related to the pathophysiological mechanisms leading to this adverse event. Histopathological studies have shown that DES with durable polymers can induce inflammation, eosinophilic

Table 5. Antiplatelet Agent Use

	BES	SES	p Value
Aspirin			
6 months	96.6%	97.4%	0.39
12 months	97.0%	96.1%	0.34
24 months	94.9%	94.2%	0.58
Clopidogrel/thienopyridine			
6 months	95.6%	95.2%	0.81
12 months	68.1%	66.5%	0.52
24 months	23.4%	24.3%	0.72

Values are percentage of n.
Abbreviations as in Table 1.

Table 4. Characteristics of Very Late Definite ST

Day	Patient ID	Stent Type	Lesion Type	DAPT	Clinical Presentation at Baseline	Clinical Presentation of ST
446	006–132	SES	De novo	Yes	Non-STEMI	Non-STEMI
515	001–190	BES	SVG	Yes	STEMI	Non-STEMI
536	002–288	SES	De novo	No	Stable angina II	Unstable angina
593	008–055	SES	SVG	No	Stable angina II	Non-STEMI
672	007–049	BES	SVG	Yes	Unstable angina IIb	Non-STEMI
714	006–36	SES	De novo	No	Stable angina III	Unstable angina

DAPT = dual antiplatelet therapy; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft; other abbreviations as in Table 1.

infiltrates, and vessel remodeling, which may allow for fibrin and platelet deposition and, in conjunction with altered flow dynamics, promote local thrombosis (22,23). The BES used in this study has a biodegradable polymer, located only on the abluminal surface of the stent. This polymer is coreleased with biolimus during a period of 6 to 9 months and degrades into carbon dioxide and water (8). After 1 year, definite stent thrombosis continued to occur with both BES (0.2%) and SES (0.5%, p = 0.42). The rate of very late definite stent thrombosis of 0.5% encountered with SES is reminiscent of the annual rate of 0.53% (95% CI: 0.44% to 0.64%) previously reported with early generation DES (24). The small and nonsignificant difference in the rates of very late definite stent thrombosis observed in the current study, however, can neither prove nor disprove the concept of a biodegradable polymer used for drug release. Longer-term follow-up and studies of larger patient populations are required to assess whether a biodegradable polymer will meaningfully influence the occurrence of very late stent thrombosis. The optimal duration of dual antiplatelet therapy after implantation of DES is not clear, and the risk of bleeding has to be balanced against the potential benefit of secondary prevention and the risk of stent thrombosis (25,26). In the present study, discontinuation of dual antiplatelet therapy before 12 months (per protocol, clopidogrel was recommended for at least 12 months) was associated with a rate of stent thrombosis in the SES group of 1.2%, whereas no event was observed in the BES group. When dual antiplatelet therapy was discontinued after 12 months, the rate of stent thrombosis was 0.6% in the SES group compared with 0% in the BES group. Whether these results in the BES group are due to the properties of the biodegradable polymer or just incidental remains speculative at this point. However, results from a substudy using optical coherence tomography imaging at 9 months revealed more complete strut coverage with BES than with SES, suggesting a difference in healing properties and therefore the potential substrate for stent thrombosis.

Conclusions

At 2 years of follow-up, the unrestricted use of BES with a biodegradable polymer maintained a similar safety and efficacy profile as SES with a durable polymer.

Reprint requests and correspondence: Prof. Stephan Windecker, Department of Cardiology, Bern University Hospital, Freiburgstrasse 10, 3010 Bern, Switzerland. E-mail: stephan.windecker@insel.ch.

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Key Words: restenosis ■ stents ■ thrombosis.